

INPLASY PROTOCOL

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submission:** Piloting of the
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Conflicts of interest:
None declared.

INTRODUCTION

Review question / Objective: Participants: adult patients with intractable epilepsy. Interventions: The test group was treated with a combination of Chinese herbs and antiepileptic drugs. Comparators: the

The Effect of Chinese Herbal Medicine Combined With Antiepileptic Drugs on Intractable Epilepsy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Review question / Objective: Participants: adult patients with intractable epilepsy. Interventions: The test group was treated with a combination of Chinese herbs and antiepileptic drugs. Comparators: the control group was treated with the antiepileptic drugs. Outcomes: The primary outcome measurement was the total effective rate. The secondary outcome measurement included the following: monthly seizure frequency; EEG abnormality rate; quality of life; seizure duration; adverse events; the evaluation proceeded at the end of the treatment course. Types of studies: randomized controlled trials (RCTs) were included in this review, in spite of blinding, publication status or language.

Information sources: The literature searches will be conducted in the following eight databases: MEDLINE, EMBASE, OVID, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (SinoMed), Wanfang Database and VIP information database. There was no restriction on language, publication date or publication status.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 November 2021 and was last updated on 11 November 2021 (registration number INPLASY2021110034).

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duration; adverse events; the evaluation proceeded at the end of the treatment course. Types of studies: randomized controlled trials (RCTs) were included in this review, in spite of blinding, publication status or language.

Condition being studied: Epilepsy affects more than 70 million people worldwide, and about 20-30% of these patients cannot be fully controlled with regular medication and develop into intractable epilepsy. Long-term recurrent of seizures increase the risk of trauma, sudden death, and asphyxia, and the long-term use of multiple antiepileptic drugs may cause adverse effects on the central nervous system and multiple systems of the patient. The treatment of traditional Chinese medicine of intractable epilepsy mostly uses a combination of Chinese and Western treatment methods, which has better efficacy and fewer side effects. In this paper, we conducted a meta-analysis of existing randomized controlled trials of Chinese herbal medicine combined with antiepileptic drugs in treatment of intractable epilepsy, and conducted an up-to-date evidence-based assessment of its efficacy and safety.

METHODS

Participant or population: Adult patients of any age, gender, or ethnic background with the main complaint of intractable epilepsy were included. Patients with a clear diagnosis of epilepsy and no significant improvement in epileptic symptoms on two or more antiepileptic drugs.

Intervention: Intervention is defined as Chinese herbal medicine at any dose, frequency, duration, and intensity. Studies that evaluated Chinese herbal medicine combined with antiepileptic drugs are also eligible.

Comparator: The comparators included placebo, no treatment, pharmacotherapy routinely used such as antiepileptic drugs. When another treatment was combined with Chinese herbal medicine, the adjunct needed to be the same as the control.

Study designs to be included: Only randomized controlled trials (RCTs) which evaluate Chinese herbal medicine combined with antiepileptic drugs in treatment of intractable epilepsy will be included in this review, regardless of blinding, publication status or language. Semi-RCTs, for example, allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study (alternation) will be excluded.

Eligibility criteria: Inclusion criteria: 1) Types of studies: randomized controlled trials (RCTs) were included in this review, in spite of blinding, publication status or language. 2) Participants: adult patients with intractable epilepsy. 3) Interventions: The test group was treated with a combination of Chinese herbs and antiepileptic drugs. 4) Comparators: the control group was treated with the antiepileptic drugs. 5) Outcomes: The primary outcome measurement was the total effective rate. The secondary outcome measurement included the following: monthly seizure frequency; EEG abnormality rate; quality of life; seizure duration; adverse events; the evaluation proceeded at the end of the treatment course.

Information sources: The literature searches will be conducted in the following eight databases: MEDLINE, EMBASE, OVID, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (SinoMed), Wanfang Database and VIP information database. There was no restriction on language, publication date or publication status.

Main outcome(s): The primary outcome measurement was the total effective rate. In Guideline for Clinical Trials of New Patent Chinese Medicines, evaluation standards for clinical therapeutic effects were as follows: (1) Control: Seizures-free; (2) Significant improvement? seizure frequency 76% to 100% reduction; (3) Moderate improvement? seizure frequency

51% to 75% reduction; (4) Mild improvement: seizure frequency 26% to 50% reduction; (5) No improvement: seizure frequency -24% to 25% reduction; (6) Deteriorate: seizure frequency increased 25%.

Additional outcome(s): The secondary outcome measurement included the following: (1) monthly seizure frequency; (2) EEG abnormality rate; (3) quality of life; (4) seizure duration; (5) adverse events.

Quality assessment / Risk of bias analysis: Two reviewers will independently assess the risk of bias for each included trial according to the Cochrane Handbook for Systematic Reviewers of Interventions version 5.1.0 (15). The items include random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and baseline data comparability (other bias). Each item will be categorized as low / unclear / high risk of bias. Disagreements will be resolved by discussion, with involvement of a third review author (Wang X) when necessary. In addition, we will use the grading of recommendations assessment, development, and evaluation (GRADE) approach to evaluate the quality of included evidences.

Strategy of data synthesis: Where trials were sufficiently alike in terms of population and comparison interventions, their results were combined. Mean differences (MD) and 95% confidence intervals (95% CI) were reported for continuous outcomes, and risk ratio (RR) and 95% confidence intervals (95% CI) were reported for dichotomous variables. We will use I^2 to assess heterogeneity between studies and defined low, medium, and high heterogeneity as 25%, 50%, and 75%, respectively. If p is less than 0.1, we assume definite heterogeneity. Where significant statistical heterogeneity was present, a random-effects model was used when combining trials.

Subgroup analysis: If the study heterogeneity is high, subgroup analyses will be performed. We will perform subgroup analyses by intervention, duration of intervention and study quality.

Sensitivity analysis: The sensitivity analysis was also performed by removing each study one at a time to evaluate the stability of the results. The Trial Sequential Analysis (TSA) was used to determine the robustness of on primary outcome and calculate the required information size (RIS) in the meta-analysis. Subgroup analysis was performed according to various types of interventions.

Country(ies) involved: China.

Keywords: intractable epilepsy; Traditional Chinese medicine; antiepileptic drugs; systematic review; meta-analysis

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